

**Supplemental Table 1: Inclusion and exclusion criteria of the clinical trial NCT04147494**

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***Inclusion criteria***

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Patients with the following cancer types:

- Breast cancer
- Colon cancer
- Esophageal cancer
- Gastric cancer
- Head and Neck cancer
- Lung cancer
- Ovarian cancer
- Pancreatic cancer
- Renal cancer
- Uterus Cancer

Patients who are scheduled to undergo surgical resection of the primary tumor and/or metastasis.

Patients are  $\geq 18$  years old at the time of the radiotracer administration.

Patient can provide written informed consent.

Patient is capable of complying with study procedures.

Patient is able to remain still for duration of imaging procedure (up to one hour).

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***Exclusion criteria***

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Patient is pregnant or nursing.

Patient has underlying disease which, based on the judgment of the investigator, might interfere with the collection of high-quality data.

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**Supplemental Table 2: Study population demographics and clinical characteristics**

Patient ID#	Age	Gender	Race	Cancer type	Organ	Histologic type	Surgical Procedure	pTNM
#001	51	M	Hispanic	Head and Neck	Oral mucosa left mandible	Squamous cell carcinoma	Left Composite Mandibulectomy With Left Neck Dissection	pT4a N0 M0
#002	71	M	Caucasian	Esophageal	Distal and mid esophagus	Squamous cell carcinoma	Esophagogastrectomy	pT1b N0 M0
#003	69	F	Caucasian	Gastric	Gastroesophageal junction	Adenocarcinoma	Not performed	NA
#004	57	M	Caucasian	Head and Neck	Left piriform sinus + cervical lymph nodes	P16+ squamous cell carcinoma	Left partial glossectomy and left neck dissection	pTx N2b M0
#005	76	M	NA	Colon	Cecum	Medullary Carcinoma	Right hemicolectomy	pT2 N0 M0
#006	55	M	African American	Colon	Cecum	Mucinous Adenocarcinoma	Right hemicolectomy	pT3 N1b M0
#007	68	F	African American	Head and Neck	Right retromolar trigone	Verrucous Squamous Cell Carcinoma	Right mandibulectomy	pT2 N0 M0
#008	36	F	Latino	Uterus	Uterus and lymph nodes	Squamous Cell Carcinoma	Bilateral Salpingectomy + left pelvic lymphadenectomy	pTx N1 M0
#009	65	M	Caucasian	Pancreatic	Pancreas, Tail	Adenocarcinoma	Partial pancreatectomy, pancreatic tail	pT2 N1 M0
#010	56	F	Caucasian	Colon	Sigmoid Colon	Adenocarcinoma	Colo-rectal anterior resection	ypT4b N0 M0
#011	65	F	Caucasian	Breast	Bilateral breasts	Invasive ductal adenocarcinoma	Bilateral Mastectomy	pT1c Nx
#012	61	M	Caucasian	Esophageal	Gastroesophageal junction	Adenocarcinoma	Esophagogastrectomy	pT3 pN2
#013	51	F	other	Breast	Right breast	Invasive ductal carcinoma	Right mastectomy and lymphadenectomy	ypT0 N0 M0
#014	73	M	Caucasian	Pancreatic	Pancreas, head	Adenosquamous carcinoma	Not performed	NA
#015	56	F	Latino	Colon	Left colon + solitary liver metastasis	Adenocarcinoma	Left hemicolectomy	ypT3 N1b M1a

**Supplemental Table 3: <sup>68</sup>Ga-FAPi-46 PET biodistribution in normal organs quantified by SUVmean (n=15 patients)**

Organ	<sup>68</sup> Ga-FAPi-46 uptake SUVmean Average ±SD (range)
1. Brain	0.03±0.04 (0-0.1)
2. Parotid	1.3±0.3 (0.8-2.0)
3. Submandibular gland	2.5±0.5 (1.5-3.3)
4. Waldeyer's ring	2.0±0.8 (1.1-4.0)
5. Thyroid	1.8±0.6 (1.0-3.5)
6. Blood pool	1.2±0.2 (0.9-1.5)
7. Heart	1.1±0.5 (0.6-2.8)
8. Lung	0.5±0.2 (0.2-1.2)
9. Liver	0.8±0.2 (0.6-1.2)
10. Gallbladder	0.7±0.2 (0.5-1.1)
11. Pancreas	2.0±1.4 (0.6-6.0)
12. Spleen	0.9±0.2 (0.6-1.2)
13. Adrenal	1.0±0.3 (0.4-1.5)
14. Kidney	2.0±0.6 (1.4-3.9)
15. Small bowel	0.8±0.2 (0.5-1.2)
16. Colon	0.8±0.4 (0.3-1.6)
17. Urinary bladder	51.9±28.4 (13.9-108.7)
18. Uterus (n=7)	6.3±3.7 (2.3-13.4)
19. Prostate (n=8)	1.2±0.4 (0.5-1.9)
20. Ovary (n=6)	1.7±0.4 (1.2-2.2)
21. Testis (n=8)	1.6±0.3 (1.2-2.1)
22. Bone marrow	0.7±0.3 (0.4-1.5)
23. Muscle	1.3±0.3 (0.9-2.2)
25. Fat	0.3±0.1 (0.2-0.7)
25. Breast (n=7)	1.4±0.8 (0.7-2.5)

**Supplemental Table 4: <sup>68</sup>Ga-FAPi-46 uptake in primary tumors (n=15 patients)**

Patient	Cancer type	Histologic type	Size (mm)	SUVmax	SUVmean
001	Head/Neck	Carcinoma cuniculatum	13	7.7	6.3
002	Esophagus	Squamous cell carcinoma	13	5.4	4.3
003*	Gastric	Adenocarcinoma	32	7.4	6.0
004	Head/Neck	P16+ squamous cell carcinoma	12	7.4	6.3
005	Colon	Medullary Carcinoma	30	8.1	6.8
006	Colon	Mucinous Adenocarcinoma	16	6.3	5.2
007	Head/Neck	Verrucous Squamous Cell Carcinoma	18	4.7	3.9
008	Uterus	Squamous Cell Carcinoma	38	19.0	15.2
009	Pancreas	Adenocarcinoma	26	15.7	12.5
010*	Colon	Adenocarcinoma	39	15.9	12.8
011	Breast	Invasive ductal adenocarcinoma	10	4.6	4.0
012*	Esophagus	Adenocarcinoma	52	9.1	7.3
013*	Breast	Invasive ductal carcinoma	-	1.7	1.4
014*	Pancreas	Adenosquamous carcinoma	13	13.4	10.6
015*	Colon	Adenocarcinoma	-	2.5	2.0
Average±SD			24±13	8.6±5.2	7.2±4.4

- = no anatomic correlation

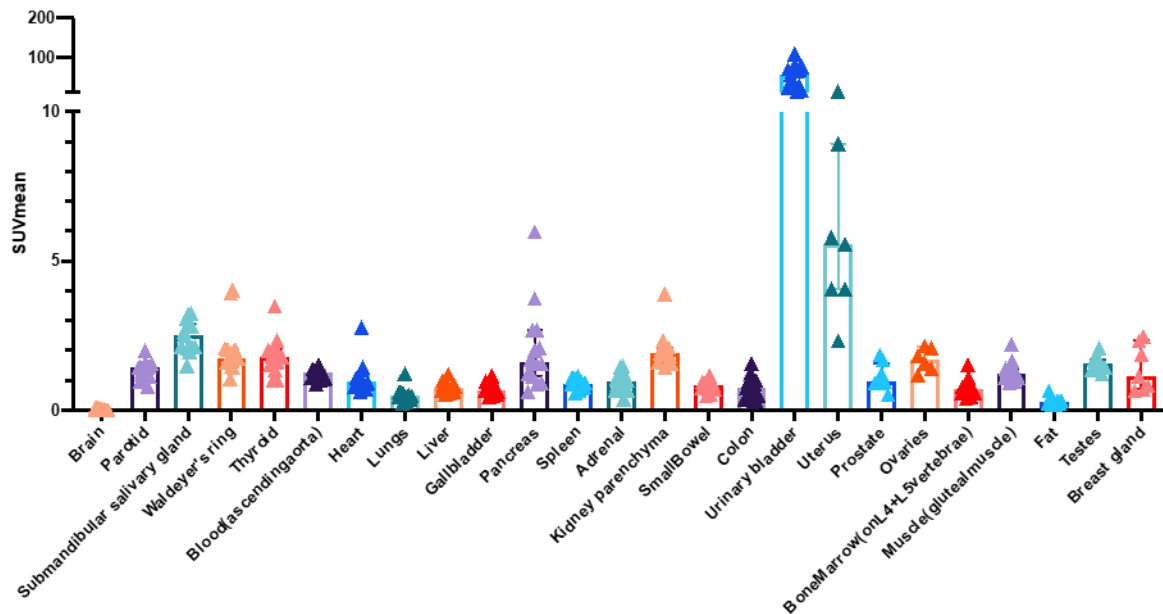
\* = Neo-adjuvant therapy

**Supplemental Table 5: <sup>68</sup>Ga-FAPi-46 uptake in metastases (n= 3 patients)**

Patient	Metastasis Site	Primary Histologic type	Size (mm)	SUVmax	SUVmean
004	Lymph node	SCC (Head/Neck)	20	5.6	4.6
004	Lymph node	SCC (Head/Neck)	20	6.8	5.5
004	Lymph node	SCC (Head/Neck)	19	7.7	6.3
008	Lymph node	SCC (uterus)	21	10.8	8.8
009	Liver	Adenocarcinoma (pancreas)	11	3.5	3.0
015	Liver	Adenocarcinoma (colon)	12	2.7	2.1
Average±SD			17.1±4.1	5.3±3.6	4.3±2.9

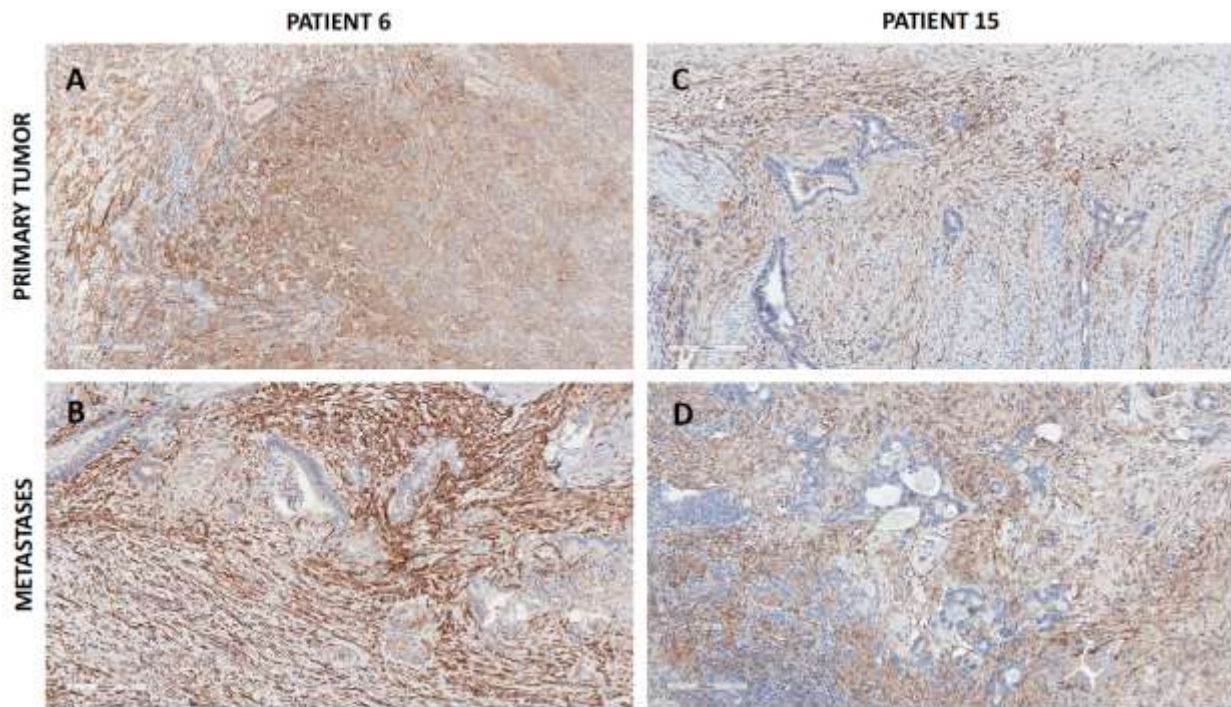
SCC: Squamous Cell Carcinoma

**Supplemental Figure 1:**  $^{68}\text{Ga}$ -FAPi-46 PET biodistribution in normal organs quantified by SUVmean (n=15 patients)



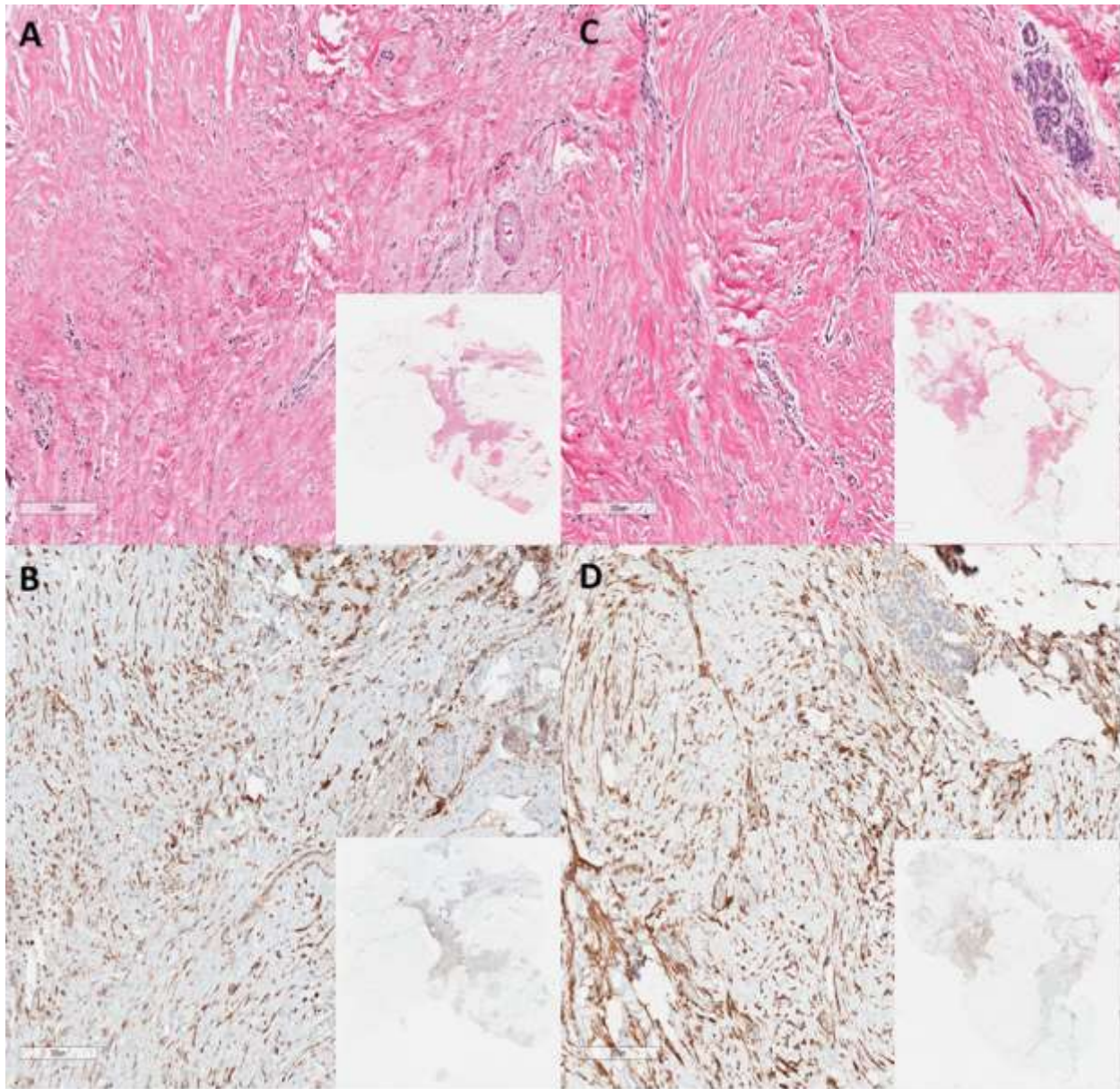
Each bar represents the average SUVmean with standard deviation error bars

**Supplemental Figure 2. Matched IHC in primary tumor and metastases in patient #006 and #015**



Concordance between IHC score in primary tumor (A, top left) and metastatic lesion (B, bottom left) from patient #006 showing moderate to strong FAP expression. Concordance between IHC score in primary lesion (C, top right) and metastatic lesion (D, bottom right) from patient #015 showing moderate FAP expression.

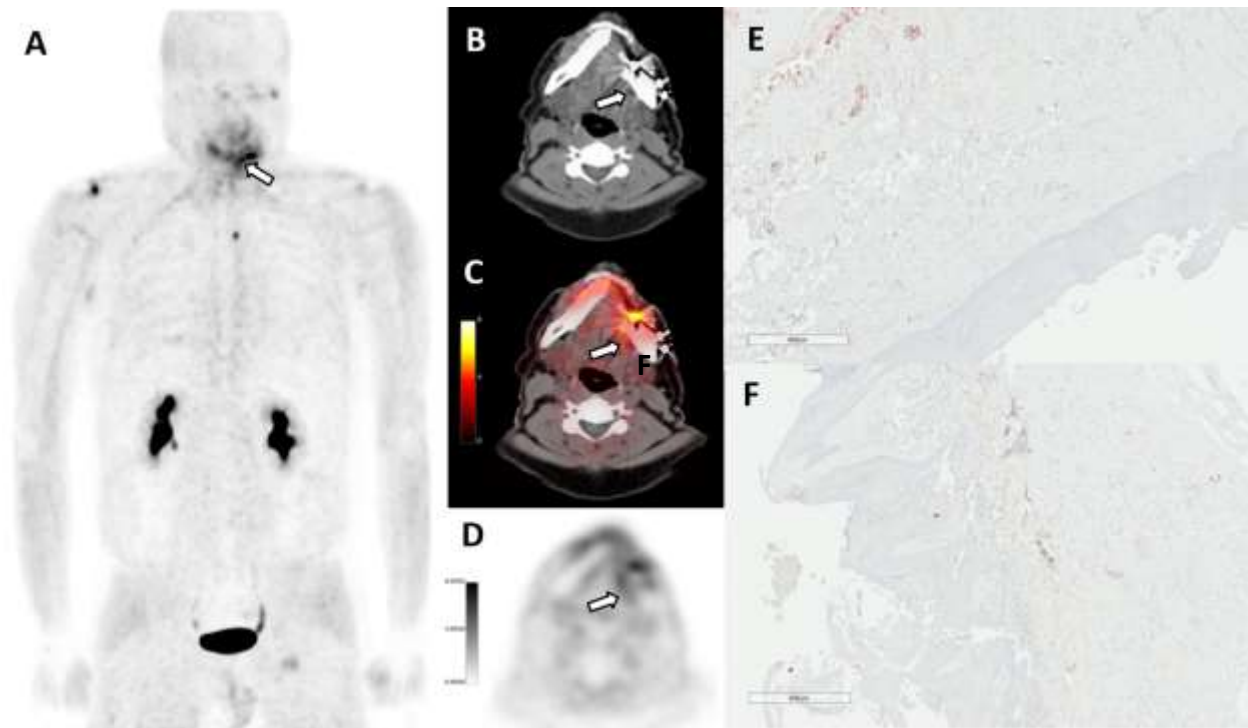
**Supplemental Figure 3: Patient #011 Breast Biopsies immunohistochemistry**



A 65-year-old female patient with 65-year-old female patient with bilateral breast invasive ductal adenocarcinoma. H&E and FAP IHC of histologic sections of left (**A** and **B**) and right (**C** and **D**) demonstrated weak to moderate FAP expression in radial scar tissues.

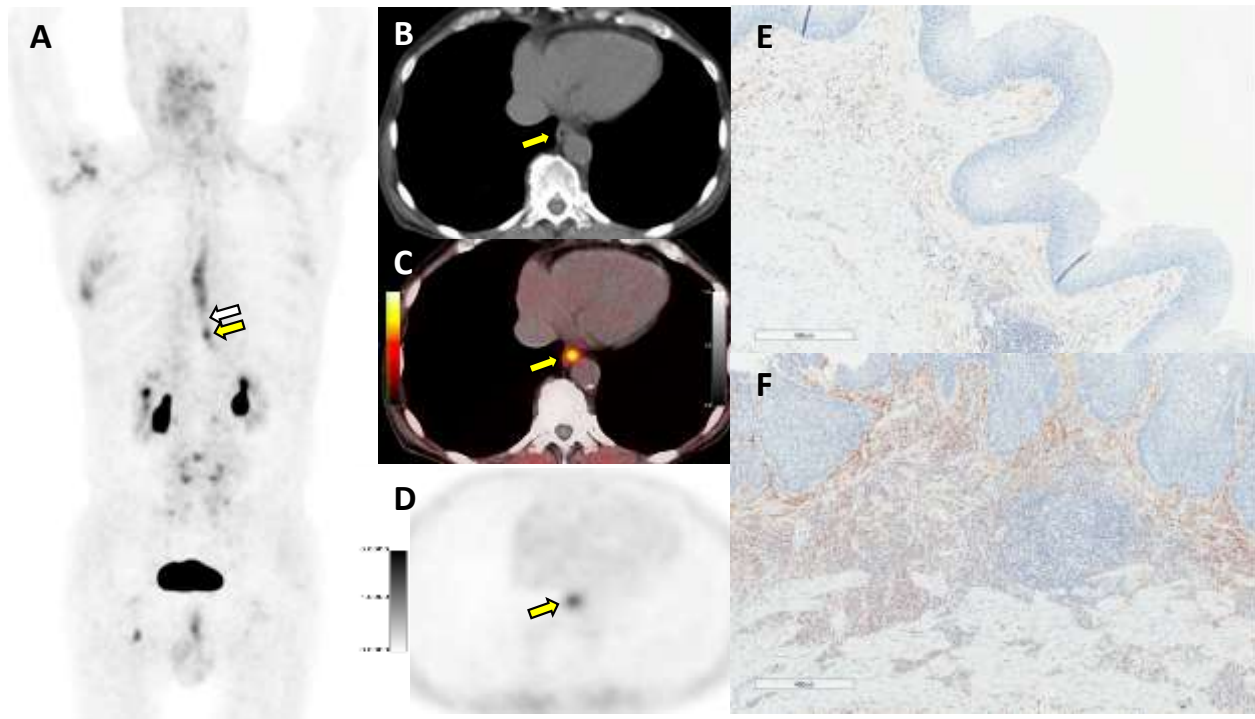


**Supplemental Figure 4: Patient #001 matched  $^{68}\text{Ga}$ -FAPi-46 PET/CT and immunohistochemistry**



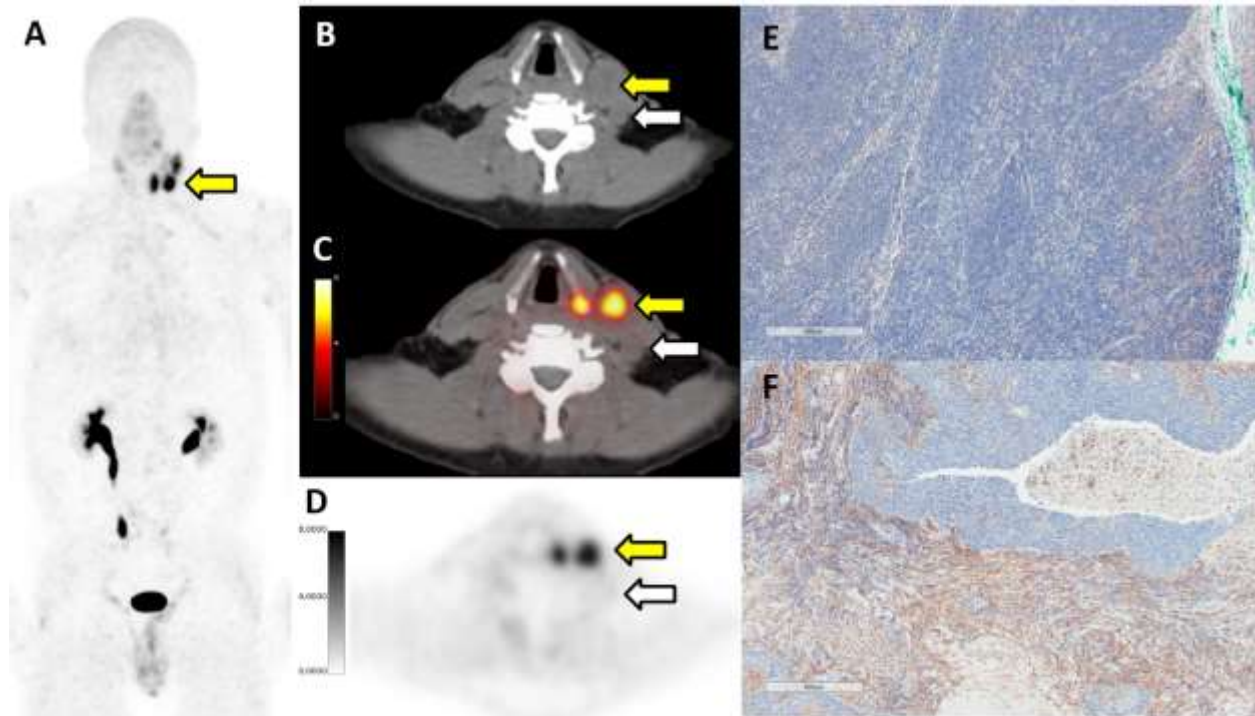
51-year-old male patient with squamous cell carcinoma (carcinoma cuniculatum) of the oral mucosa who underwent left composite mandibulectomy with left neck dissection (pT4a N0 M0). In correspondence of the resected lesion as shown by the white arrows,  $^{68}\text{Ga}$ -FAPi-46 PET/CT showed moderate diffuse increased signal (**A**: Maximum Intensity Projection (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 7.7 and SUVmean 6.3, respectively). FAP IHC on representative histologic sections of normal (**E**) and tumor (**F**) tissue demonstrated absent FAP expression in both, indicative of either a histologic sampling bias or PET overcorrection artefact from dense material.

**Supplemental Figure 5: Patient #002 matched  $^{68}\text{Ga}$ -FAPI-46 PET/CT and immunohistochemistry**



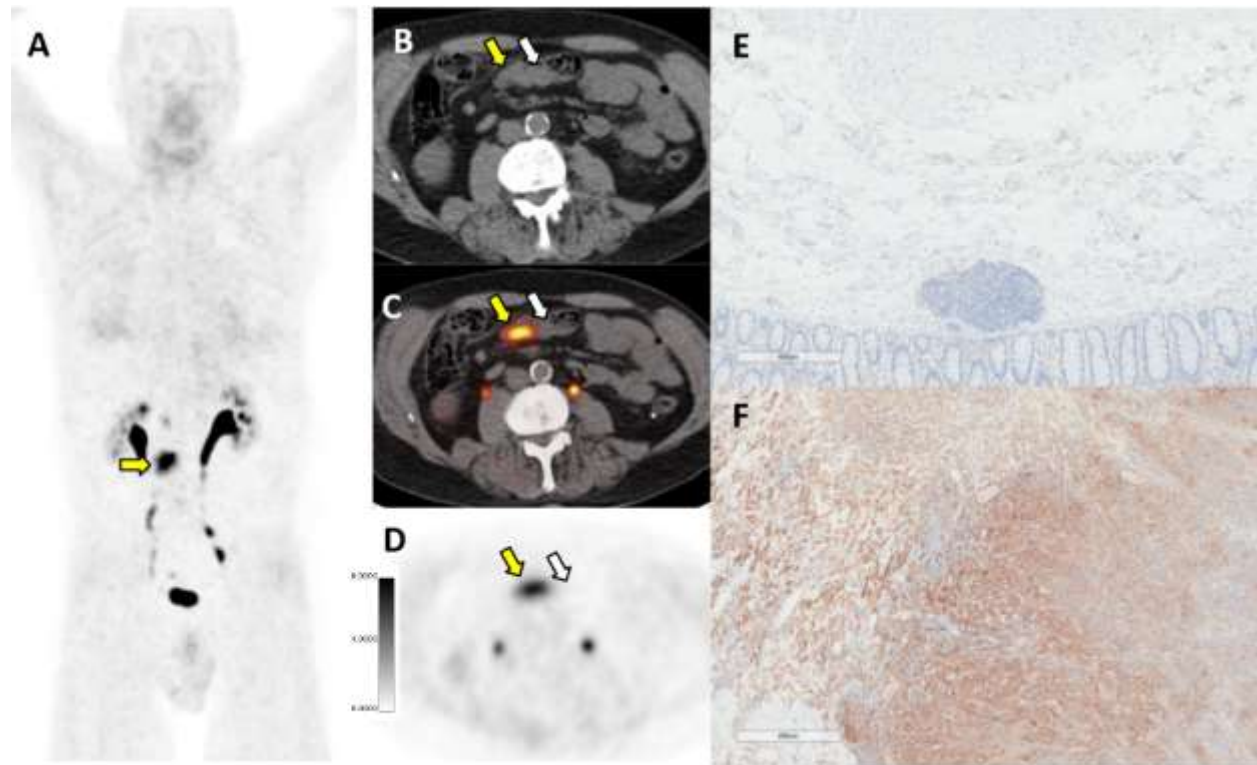
71-year-old male patient with esophageal adenocarcinoma who underwent esophagogastrectomy (pT1b N0 M0). In correspondence of the resected lesion as shown by the yellow arrows,  $^{68}\text{Ga}$ -FAPI-46 PET/CT showed moderate focal uptake (**A**: Maximum Intensity Projection (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 5.4 and SUVmean 4.3, respectively). FAP IHC on representative histologic sections demonstrated absent to patchy and weak FAP expression for normal tissue (**E**) and weak to moderate FAP expression for tumor tissue (**F**). White arrow depicts resected non-cancer esophagus region.

**Supplemental Figure 6: Patient #004 matched <sup>68</sup>Ga-FAPi-46 PET/CT and immunohistochemistry**



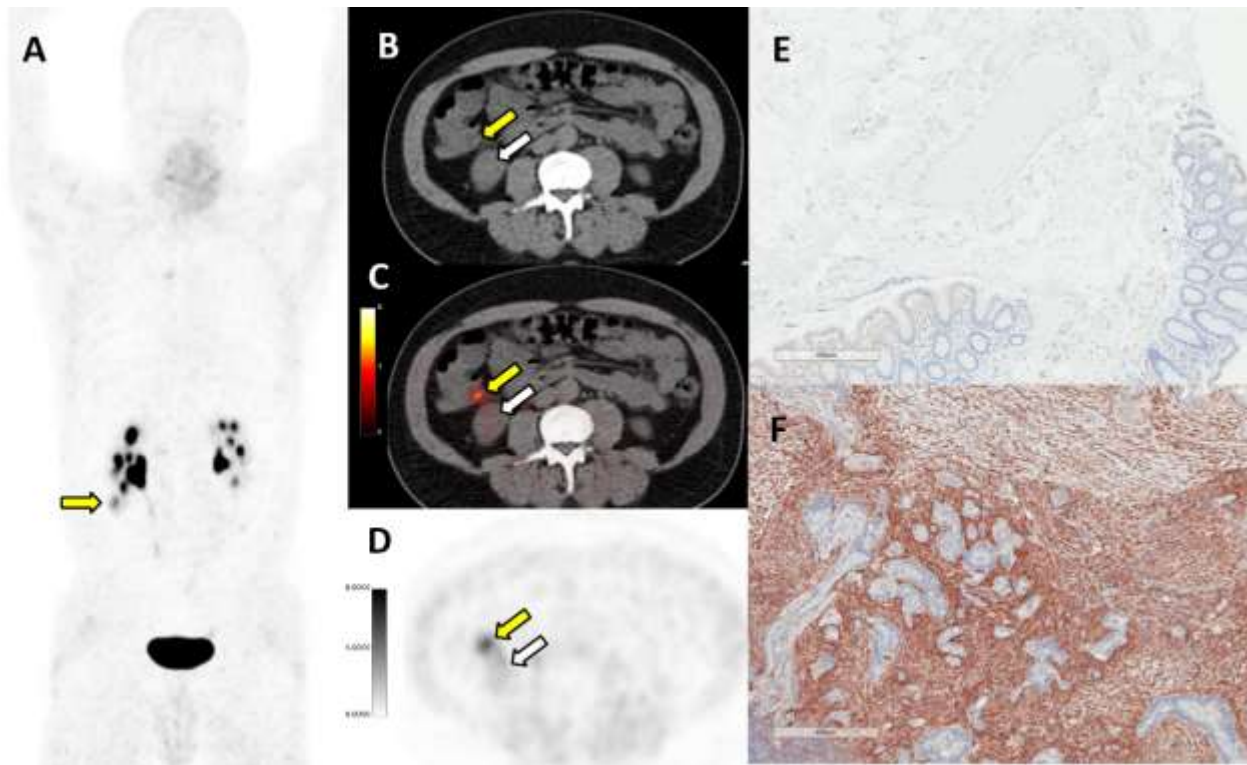
57-year-old male patient with head-and-neck squamous cell carcinoma cancer who underwent left partial glossectomy and left neck dissection (pTx N2b M0). In correspondence of the resected enlarged neck lymph nodes as shown by the yellow arrows <sup>68</sup>Ga-FAPi-46 PET/CT showed intense uptake (**A**: Maximum Intensity Projection (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and CT, SUVmax 7.4 and SUVmean 6.3, respectively). FAP IHC on representative histologic sections demonstrated no FAP expression in normal tissue (**E**) and moderate to strong FAP expression in tumor tissue (**F**). White arrows depict resected normal lymph node.

**Supplemental Figure 7: Patient #005 matched  $^{68}\text{Ga}$ -FAPi-46 PET/CT and immunohistochemistry**



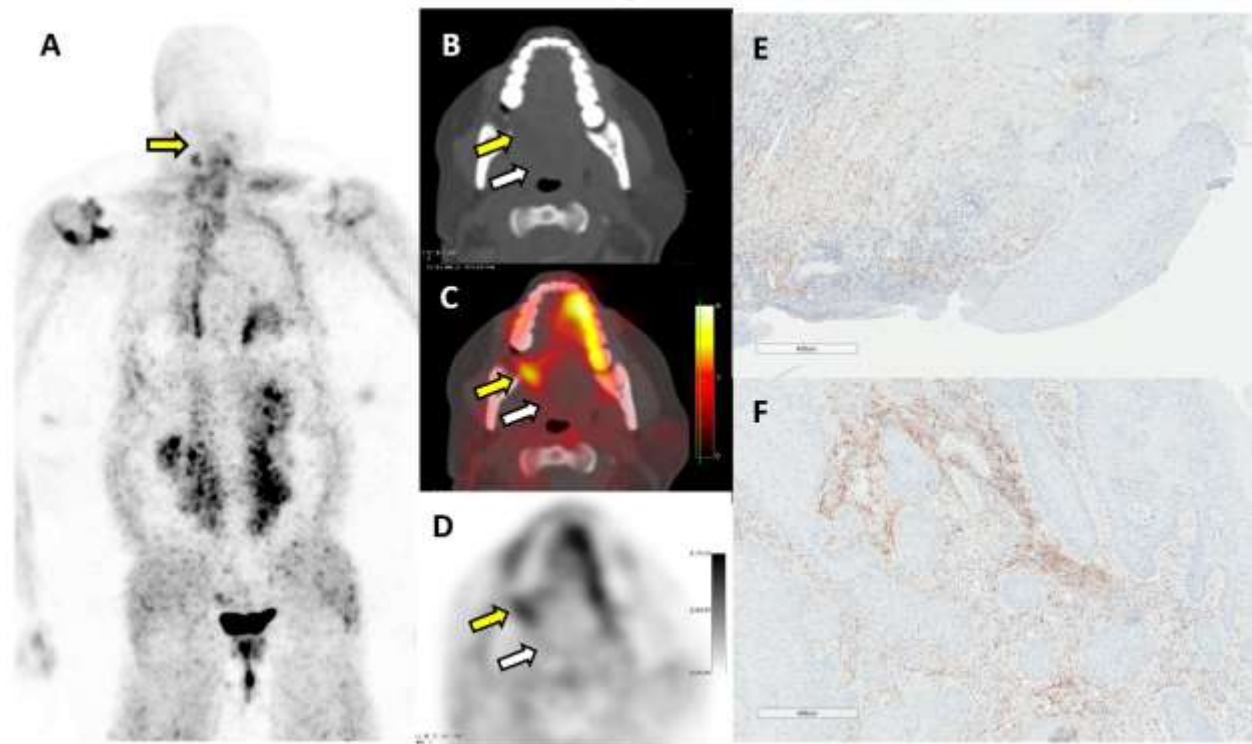
57-year-old male patient with medullary adenocarcinoma of the cecum who underwent right hemicolectomy (pT2 N0 M0). In correspondence of the resected lesion as shown by the yellow arrows  $^{68}\text{Ga}$ -FAPi-46 PET/CT showed intense uptake (**A**: Maximum Intensity Projection (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and CT, SUVmax 8.1 and SUVmean 6.8, respectively). FAP IHC on representative histologic sections demonstrated no FAP expression in normal tissue (**E**) and moderate to strong FAP expression in tumor tissue (**F**). White arrows depict resected normal colon region.

**Supplemental Figure 8: Patient #006 matched  $^{68}\text{Ga}$ -FAPi-46 PET/CT and immunohistochemistry**



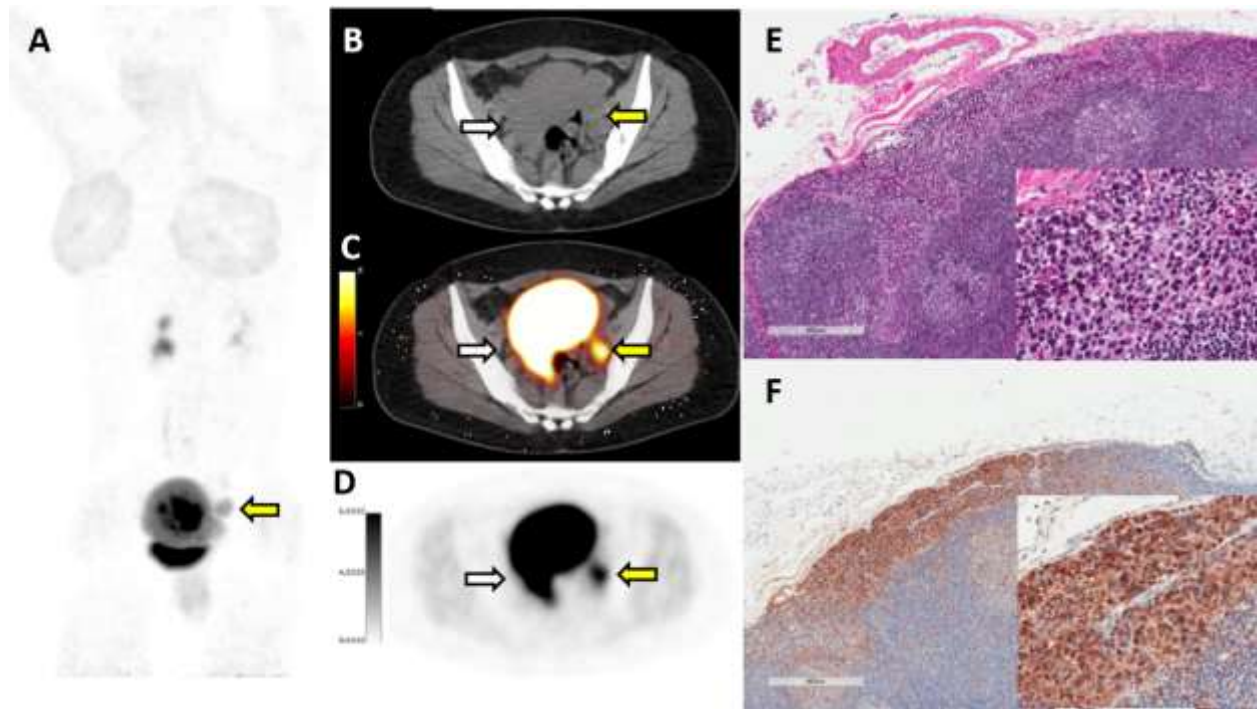
55-year-old male patient with mucinous adenocarcinoma of the cecum who underwent right hemicolectomy (pT3 N1b M0). In correspondence of the resected lesion as shown by the yellow arrows,  $^{68}\text{Ga}$ -FAPi-46 PET/CT showed increased focal uptake (**A**: Maximum Intensity Projection images (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 6.3 and SUVmean 5.2, respectively). FAP IHC on representative histologic sections demonstrated no FAP expression in normal tissue (**E**) and strong FAP expression in tumor tissue (**F**). White arrows depict normal region resected.

**Supplemental Figure 9: Patient #007 matched  $^{68}\text{Ga}$ -FAPi-46 PET/CT and immunohistochemistry**



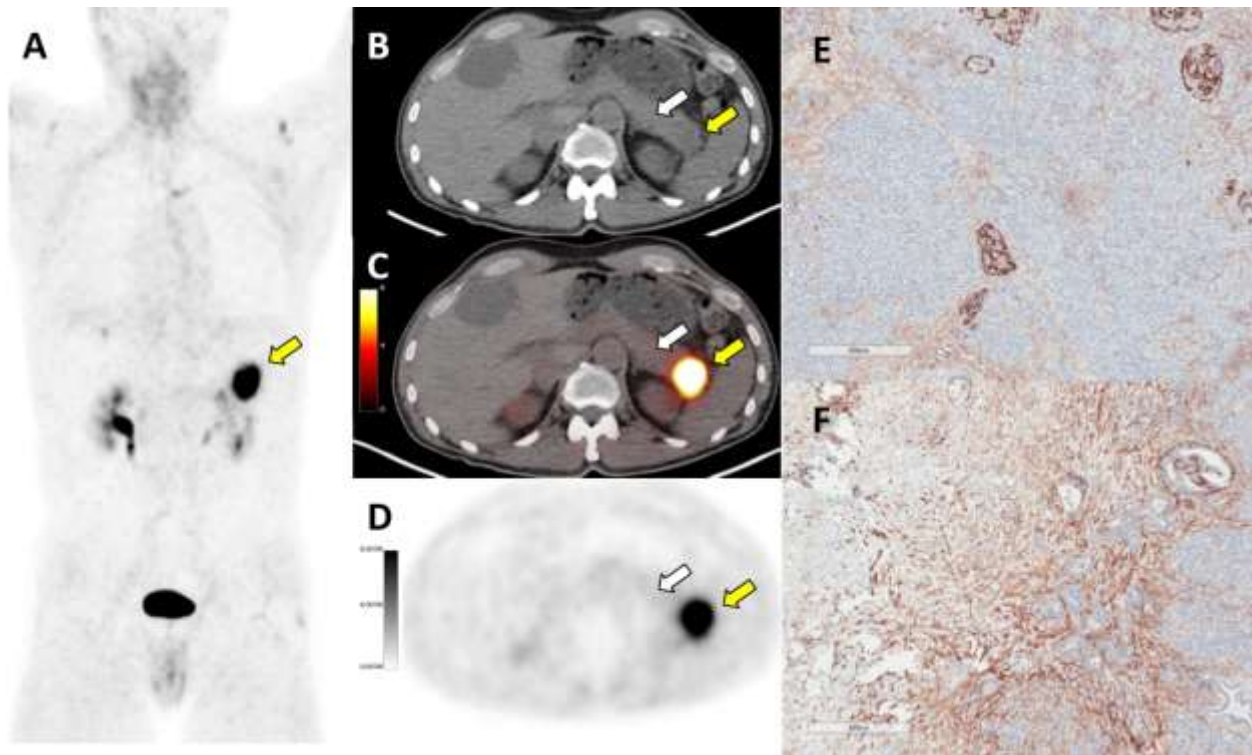
68-year-old female patient with verrucous squamous cell carcinoma of the right retromolar trigone who underwent right mandibulectomy (pT2 N0 M0). In correspondence of the resected lesion as shown by the yellow arrows,  $^{68}\text{Ga}$ -FAPi-46 PET/CT showed moderate uptake (**A**: Maximum Intensity Projection images (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 4.7 and SUVmean 3.9, respectively). FAP IHC on representative histologic sections demonstrated variable negative to weak FAP expression in normal tissue in an area notable for ulceration (**E**) and moderate FAP expression for tumor tissue (**F**). White arrows depict resected normal mucosa region.

**Supplemental Figure 10: Patient #008 matched  $^{68}\text{Ga}$ -FAPi-46 PET/CT and immunohistochemistry**



36-year-old female patient with uterine squamous cell carcinoma who underwent Bilateral Salpingectomy + left pelvic lymphadenectomy (pTx N1 M0). In correspondence of the uterus lesion and the enlarged left pelvic lymph node involved by metastatic squamous cell carcinoma as shown by the yellow arrows,  $^{68}\text{Ga}$ -FAPi-46 PET/CT showed intense uptake (**A**: Maximum Intensity Projection images (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 19 and SUVmean 15.2, respectively). H&E (**E**) and FAP IHC staining (**F**) on histologic section of a representative lymph node revealed moderate to strong FAP staining of tumor cells metastasizing to the lymph node. White arrows depict resected normal contralateral lymph node.

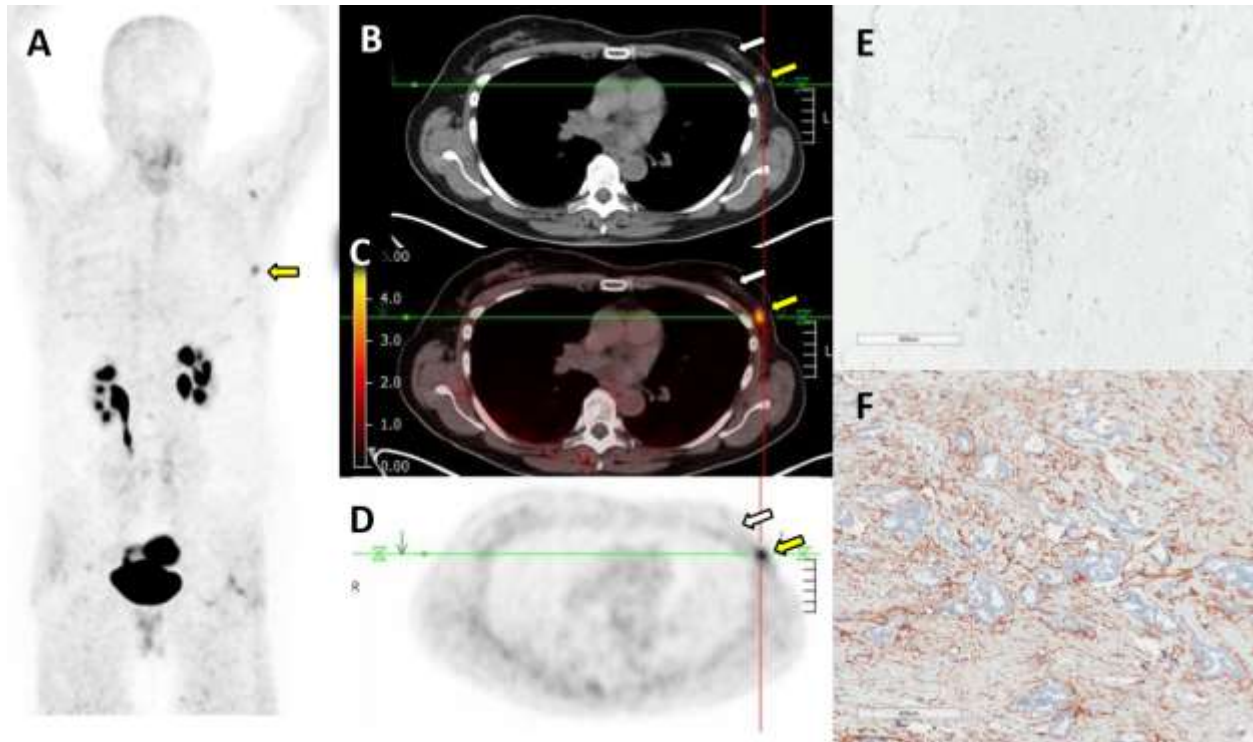
**Supplemental Figure 11: Patient #009 matched  $^{68}\text{Ga}$ -FAPi-46 PET/CT and immunohistochemistry**



65-year-old male patient with pancreatic ductal adenocarcinoma who underwent partial pancreatectomy, of the pancreatic tail (pT2 N1 M0). In correspondence of the resected lesion as shown by the yellow arrows,  $^{68}\text{Ga}$ -FAPi-46 PET/CT showed intense uptake (**A**: Maximum Intensity Projection images (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 15.7 and SUVmean 12.5, respectively). FAP IHC on representative histologic sections demonstrated variable negative to weak FAP expression in normal pancreatic parenchyma with a subpopulation of cells in normal islets consistently showing strong FAP expression (**E**). Moderate to strong FAP expression was noted for tumor tissue (**F**). White arrows depict resected normal pancreas region.

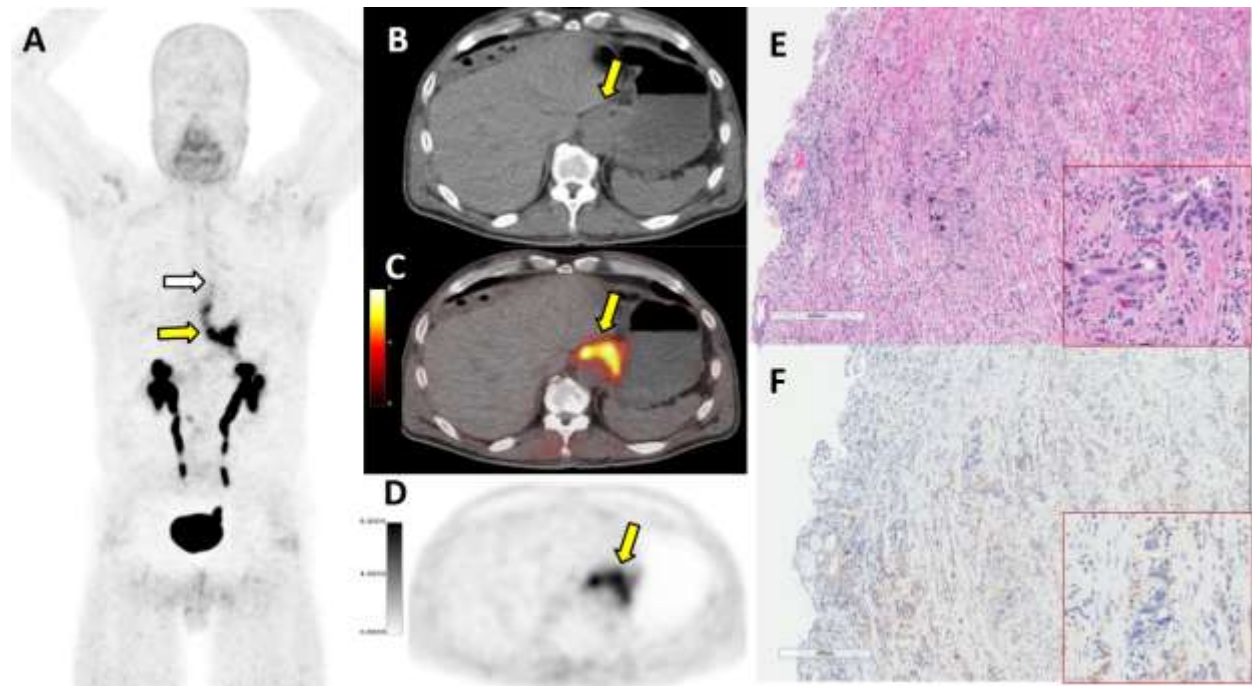


**Supplemental Figure 12: Patient #011 matched  $^{68}\text{Ga}$ -FAPi-46 PET/CT and immunohistochemistry**



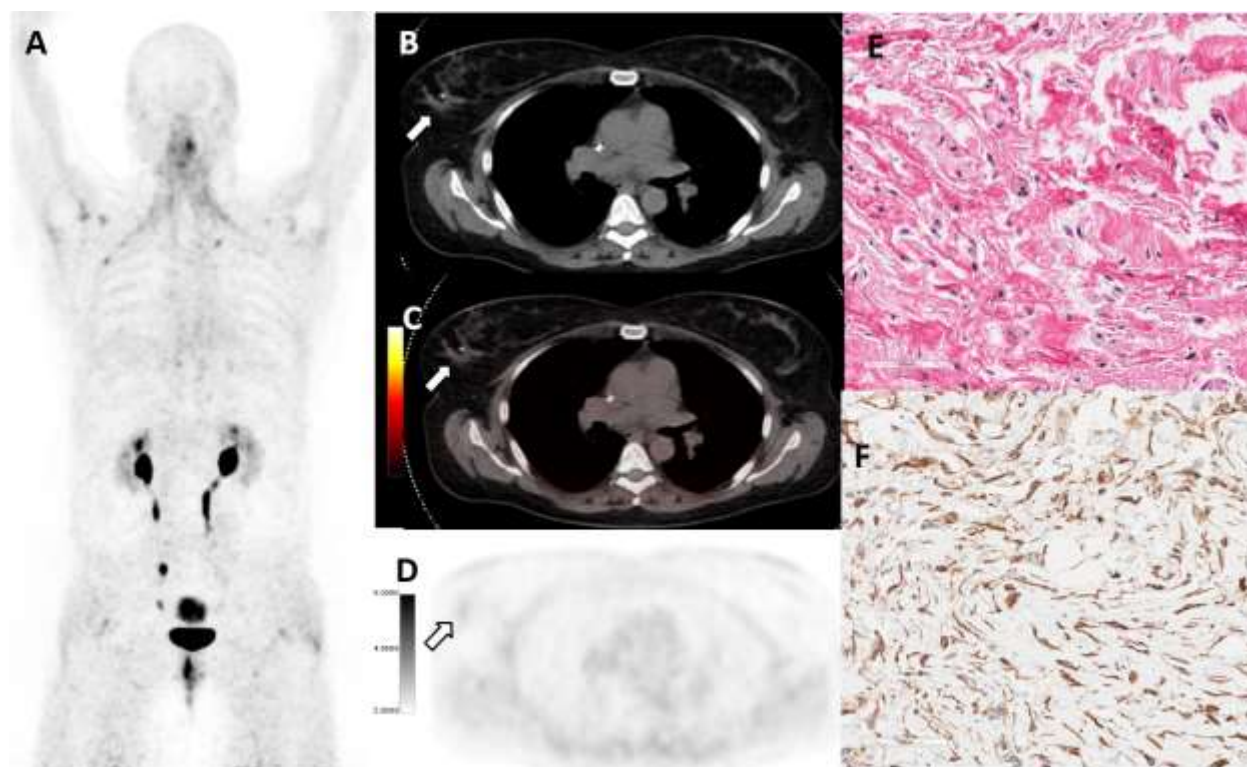
65-year-old female patient with bilateral breast invasive ductal adenocarcinoma who underwent bilateral mastectomy (pT1c Nx M0). In correspondence of the resected lesion as shown by the yellow arrows,  $^{68}\text{Ga}$ -FAPi-46 PET/CT showed moderate uptake (**A**: Maximum Intensity Projection images (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 4.6 and SUVmean 4.0, respectively). FAP IHC on representative histologic sections demonstrated absent to weak FAP expression for normal tissue (**E**) and moderate to strong FAP expression for tumor tissue (**F**). White arrows depict resected normal breast region.

**Supplemental Figure 13: Patient #012 matched  $^{68}\text{Ga}$ -FAPi-46 PET/CT and immunohistochemistry**



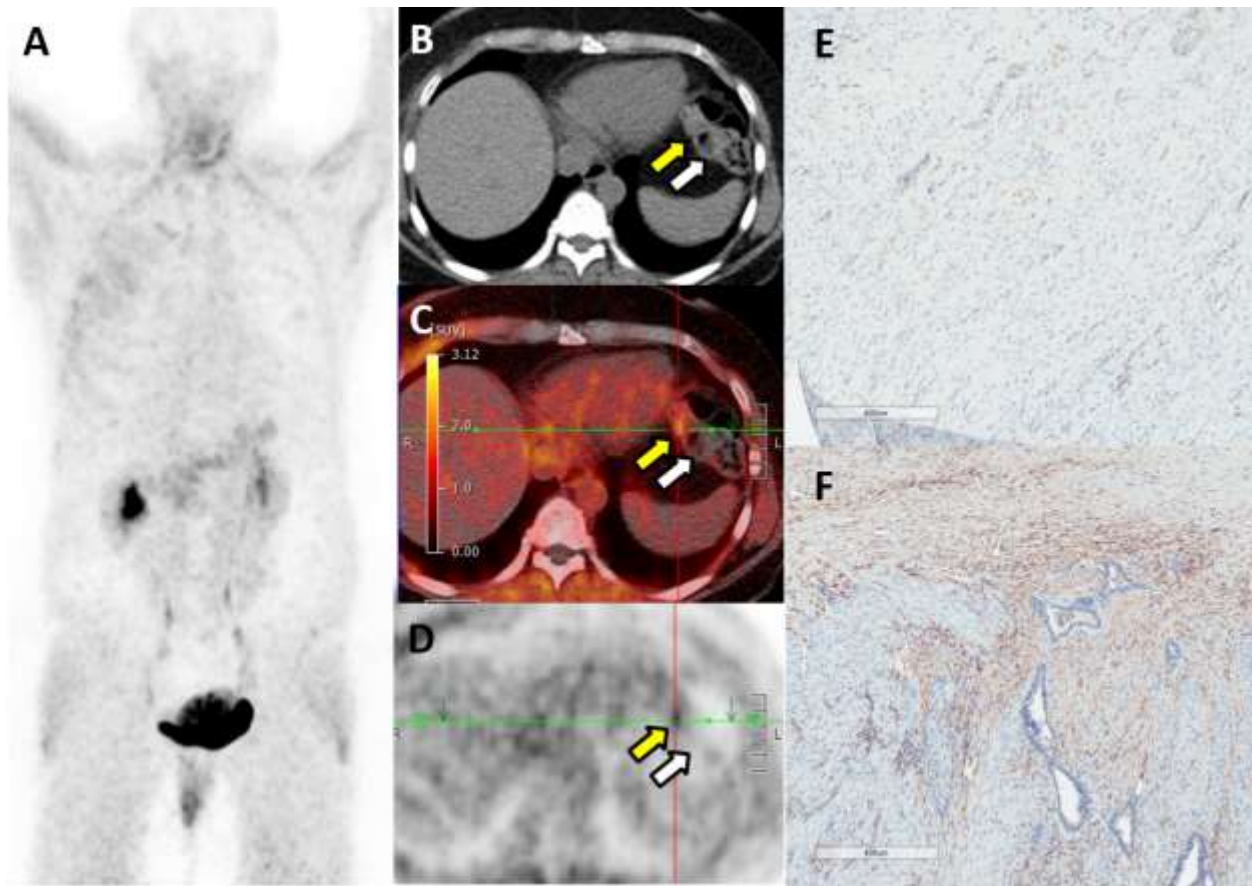
61-year-old male patient with adenocarcinoma of the gastroesophageal junction who underwent esophagogastrectomy (pT3 pN2). In correspondence of the resected lesion as shown by the yellow arrows,  $^{68}\text{Ga}$ -FAPi-46 PET/CT showed intense uptake (**A**: Maximum Intensity Projection images (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 9.1 and SUVmean 7.3, respectively). H&E (**E**) and FAP IHC staining (**F**) on histologic section of the residual small focus of adenocarcinoma revealed weak FAP staining of stroma and vessel endothelium immediately adjacent to and more distant from the tumor cells. White arrow depicts resected normal esophagus region.

**Supplemental Figure 14: Patient #013 matched PET/CT and immunohistochemistry**



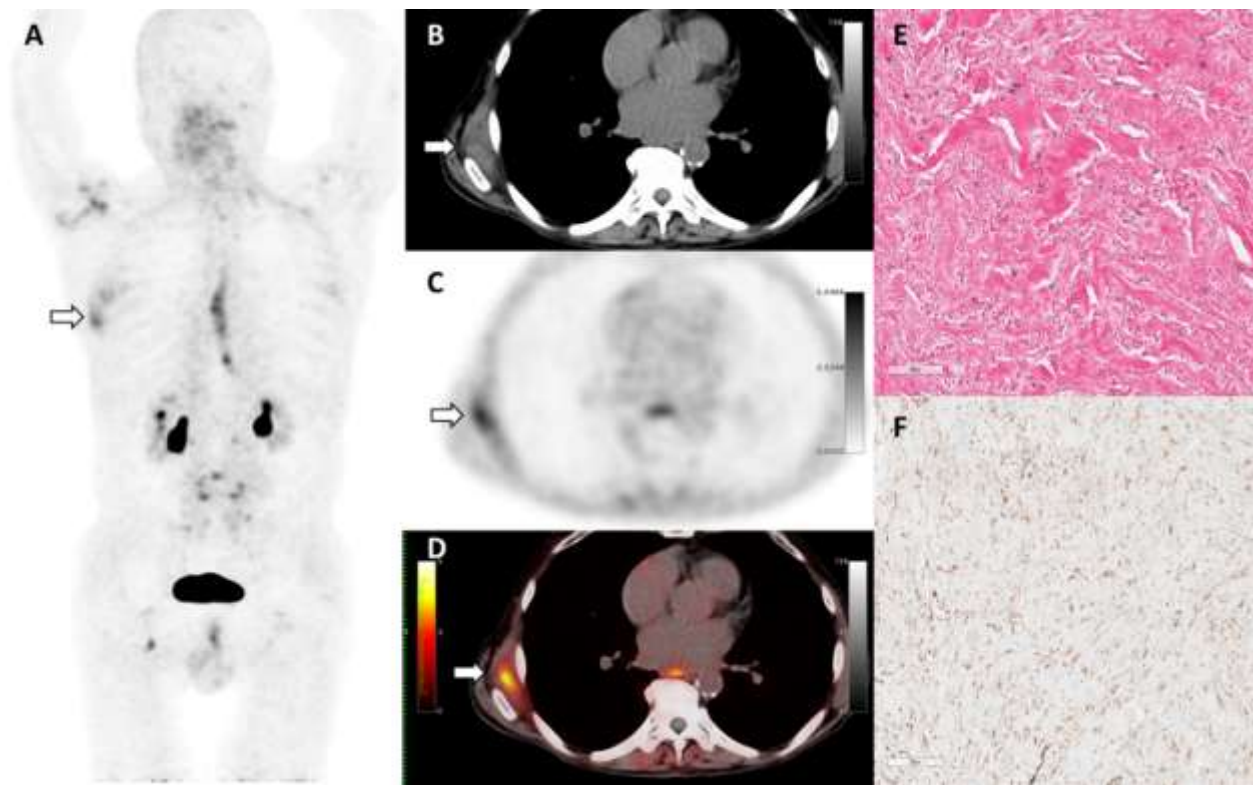
51-year-old female patient with right breast invasive ductal adenocarcinoma who underwent right mastectomy and lymphadenectomy (ypT0 N0 M0). In correspondence of the resected lesion as shown by the white arrows,  $^{68}\text{Ga}$ -FAPi-46 PET/CT showed no increased uptake (**A**: Maximum Intensity Projection images (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 1.7 and SUVmean 1.4, respectively). H&E (**E**) and FAP IHC staining (**F**) demonstrated moderate FAP expression in the area of the lesion that on histologic sections revealed a complete response to neoadjuvant therapy with no residual viable tumor.

**Supplemental Figure 15: Patient #015 matched  $^{68}\text{Ga}$ -FAPi-46 PET/CT and immunohistochemistry**



56-year-old female patient with left colon adenocarcinoma with liver metastasis who underwent left hemicolectomy (ypT3 N1b M1a). In correspondence of the resected lesion as shown by the yellow arrows,  $^{68}\text{Ga}$ -FAPi-46 PET/CT showed moderate uptake (**A**: Maximum Intensity Projection images (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 2.5 and SUVmean 2.0, respectively). FAP IHC on representative histologic sections of the muscularis propria of the bowel wall demonstrated absent to weak FAP expression in vessel endothelium for normal tissue (**E**) and moderate expression for tumor tissue (**F**). White arrows depict normal region resected.

**Supplemental Figure 16: Patient #002 Elastofibroma Dorsi matched  $^{68}\text{Ga}$ -FAPi-46 PET/CT and immunohistochemistry**



A 71-year-old male patient with a right sub-scapula elastofibroma dorsi underwent  $^{68}\text{Ga}$ -FAPi-46 PET/CT. In correspondence of the resected lesion as shown by the white arrows,  $^{68}\text{Ga}$ -FAPi-46 PET/CT showed moderate diffuse increased uptake (**A**: Maximum Intensity Projection images (MIP), **B**: transaxial CT, **C** and **D**: transaxial PET/CT and PET, SUVmax 5.4 and SUVmean 4.3, respectively). H&E and FAP IHC of histologic sections of the benign elastofibroma (**E** and **F**) revealed weak FAP expression.

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